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Integration of Vestibular and Gastrointestinal Inputs by Cerebellar Fastigial Nucleus Neurons: Multisensory Influences on Motion Sickness

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Abstract

Previous studies demonstrated that ingestion of the emetic compound copper sulfate (CuSO_4) alters the responses to vestibular stimulation of a large fraction of neurons in brainstem regions that mediate nausea and vomiting, thereby affecting motion sickness susceptibility. Other studies suggested that the processing of vestibular inputs by cerebellar neurons plays a critical role in generating motion sickness, and that neurons in the cerebellar fastigial nucleus receive visceral inputs. These findings raised the hypothesis that stimulation of gastrointestinal receptors by a nauseogenic compound affects the processing of labyrinthine signals by fastigial nucleus neurons. We tested this hypothesis in decerebrate cats by determining the effects of intragastric injection of CuSO_4 on the responses of rostral fastigial nucleus to whole-body rotations that activate labyrinthine receptors. Responses to vestibular stimulation of fastigial nucleus neurons were more complex in decerebrate cats than reported previously in conscious felines. In particular, spatiotemporal convergence (STC) responses, which reflect the convergence of vestibular inputs with different spatial and temporal properties, were more common in decerebrate than in conscious felines. The firing rate of a small percentage of fastigial nucleus neurons (15%) was altered over 50% by the administration of CuSO_4 ; the firing rate of the majority of these cells decreased. The responses to vestibular stimulation of a majority of these cells were attenuated after the compound was provided. Although these data support our hypothesis, the low fraction of fastigial nucleus neurons whose firing rate and responses to vestibular stimulation were affected by the administration of CuSO_4 cast doubt on the notion that nauseogenic visceral inputs modulate motion sickness susceptibility principally through neural pathways that include the cerebellar fastigial nucleus. Instead, it appears that convergence of gastrointestinal and vestibular inputs occurs mainly in the brainstem.

Keywords

Vomiting; nausea; emesis; multisensory integration; copper sulfate; gastrointestinal receptors; cerebellum

Introduction

Motion sickness is triggered by sensory conflict, when sensory inputs provide contradictory information regarding body motion in space or information that deviates from that experienced in the past during the same movement (Reason and Brandt 1975; Reason 1978). Since the cerebellum integrates labyrinthine and nonlabyrinthine inputs that reflect body position in space, it has long been hypothesized as playing a major role in generating motion sickness (Cohen et al. 2003; Cohen et al. 2008; Yates et al. 2014). This notion is supported by considerable experimental evidence. Lesion studies showed that animals with ablation of the posterior cerebellar vermis no longer vomited during provocative motion that previously elicited emesis (Bard et al. 1947; Tyler and Bard 1949; Wang and Chinn 1956). In addition, the posterior cerebellar vermis plays a key role in velocity storage, an integrative process that has been linked to motion sickness (Cohen et al. 2003; Cohen et al. 2008). Velocity storage serves to adjust the dynamic range of the vestibulo-ocular reflex, so it accurately compensates for ongoing head movements. Drugs that suppress motion sickness also have a correlated effect on the time constant of velocity storage, indicating that the two processes are related (Cohen et al. 2008).

Although some Purkinje cells in the posterior cerebellar vermis project directly to the vestibular nuclei, (Angaut and Brodal 1967; Precht et al. 1976; Shojaku et al. 1987; Walberg and Dietrichs 1988; Paton et al. 1991), the output of this region to the brainstem is principally relayed through a deep cerebellar nucleus, the fastigial nucleus (Ruggiero et al. 1977). The rostral fastigial nucleus projects to the caudal aspect of the vestibular nucleus complex (Carleton and Carpenter 1983; Andrezik et al. 1984; Homma et al. 1995), which makes connections with brainstem regions believed to participate in generating nausea and vomiting, including nucleus tractus solitarius (Balaban and Beryozkin 1994; Yates et al. 1994; Porter and Balaban 1997; Aleksandrov et al. 1998; Cai et al. 2007) and the lateral tegmental field (Yates et al. 1995). The latter area was historically called the “vomiting center,” as a variety of experimental approaches showed that it plays a critical role in generating emesis (for review, see (Yates et al. 2014)). In addition, the fastigial nucleus projects directly to the lateral aspect of nucleus tractus solitarius (Homma et al. 1995). Thus, the connections of the rostral fastigial nucleus are appropriate for this neural region to participate in the generation of motion sickness.

In addition to processing labyrinthine inputs, rostral fastigial nucleus neurons receive visceral signals, both directly from brainstem nuclei (Zheng et al. 1982; Shapiro and Miselis 1985) and relayed through the posterior cerebellar vermis (Somana and Walberg 1979; Shapiro and Miselis 1985; Okahara and Nisimaru 1991; Tong et al. 1993; Saab and Willis 2001). In a series of experiments, we have investigated the effects of intragastric injection of the emetic compound copper sulfate (CuSO_4) on the processing of vestibular signals by brainstem regions that mediate nausea and vomiting (Sugiyama et al. 2011; Moy et al. 2012; Suzuki et al. 2012; Arshian et al. 2013). The responses to whole-body rotations that activate labyrinthine receptors of neurons in some of these areas, particularly the parabrachial nucleus (Suzuki et al. 2012) and the lateral tegmental field (Moy et al. 2012), were profoundly altered when CuSO_4 was present in the stomach. These findings suggest that activation of visceral receptors affects motion sickness susceptibility by altering the

processing of vestibular inputs in the pathways that mediate nausea and vomiting. Considering the connections of the fastigial nucleus discussed above, it is feasible that this region also participates in adjusting motion sickness susceptibility when animals are nauseated by a stimulus that activates visceral receptors.

The primary hypothesis tested in this study was that intragastric injection of the emetic compound CuSO₄ alters the responses of fastigial nucleus neurons to whole-body rotations in vertical planes that activate vestibular receptors. As in our previous studies that considered the effects of CuSO₄ administration on the processing of labyrinthine inputs (Sugiyama et al. 2011; Moy et al. 2012; Suzuki et al. 2012; Arshian et al. 2013), recordings were conducted in decerebrate cats. We focused the recordings on the rostral portion of the fastigial nucleus, which plays a primary role in spatial orientation (Buttner et al. 1991; Thach et al. 1992; Siebold et al. 1997; Mori et al. 1998; Mori et al. 2004), in contrast to the caudal aspect of the fastigial nucleus whose physiological role is related to the control of eye movements (Gardner and Fuchs 1975; Buttner et al. 1991; Robinson and Fuchs 2001; Brettler and Fuchs 2002; Shaikh et al. 2005). A secondary goal of this study was to document the responses of rostral fastigial nucleus neurons to vestibular stimulation, which has not yet been thoroughly done in decerebrate cats. A previous study from our laboratory conducted in conscious cats reported the effects of whole-body rotations in vertical planes on the activity of fastigial nucleus neurons (Miller et al. 2008b). Our secondary objective was to determine the effects of decerebration on the responses, to allow comparisons between data collected using the two preparations.

Methods and materials

Data were collected from 16 laboratory bred (Liberty Research, Waverly, NY) male cats weighing 2.8–3.8 Kg (median 3.5 kg). The University of Pittsburgh's Institutional Animal Care and Use Committee (IACUC) prospectively approved all procedures on animals, which were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, National Academies Press, Washington D.C., 2011). The experimental protocol used in these experiments has been validated and thoroughly described in previous manuscripts (Sugiyama et al. 2011; Moy et al. 2012; Suzuki et al. 2012; Arshian et al. 2013), and thus will only be briefly described below.

Animals were anesthetized using isoflurane vaporized in oxygen. One femoral vein was cannulated to provide for intravenous (i.v.) injections, and a Millar (Houston, TX) Mikro-Tip[®] pressure transducer was inserted through the femoral artery into the abdominal aorta. A tracheostomy was performed, and an intragastric catheter was inserted through an esophagostomy to administer CuSO₄. Animals were placed in a stereotaxic frame with the head pitched down 30° to vertically align the anterior and posterior semicircular canals. Both carotid arteries were ligated, and a midcollicular decerebration was performed. Subsequently, the midline cerebellum was exposed, and the dura matter was opened. After all surgical procedures were completed, anesthesia was removed, and animals were paralyzed using 0.1 mg/kg injections of vecuronium bromide every 20 min. Paralyzed animals received positive-pressure artificial ventilation such that end-tidal CO₂ remained

near 4%. At the end of experiments, animals were euthanized using Euthasol Euthanasia solution.

The stereotaxic frame holding the animals was mounted on a servo-controlled hydraulic tilt table (Neurokinetics, Pittsburgh, PA). Extracellular recordings of neuronal activity were performed during whole-body rotations using 4–6M Ω tungsten microelectrodes (FHC, Bowdoin, ME). Electrodes were maneuvered using a David Kopf Instruments (Tujunga, California) model 650 hydraulic microdrive. Neuronal activity was sampled at 25,000 Hz, and blood pressure and tilt table position were sampled at 100 Hz, using a Cambridge Electronic Design (Cambridge, UK) 1401 data collection system and Spike2 version 6 software. Neuronal recordings were sampled at high frequency, so that the activity of each neuron could be discriminated on the basis of action potential shape and amplitude using the Spike2 software.

When one or more neurons were isolated, we first determined their responses to wobble stimuli (Schor et al. 1984), fixed amplitude tilts whose direction rotated about the animal at constant speed. Wobble stimuli were used to determine each unit's response vector orientation, the direction of tilt producing maximal modulation of firing rate. Response vector orientations were verified by comparing responses to tilts in the roll and pitch planes. Subsequently, fixed-plane tilts were delivered near the plane of the response vector orientation, at frequencies of 0.05–1 Hz and amplitudes of 2.5–7.5°, to determine the response dynamics for each unit. Examples of responses to fixed-plane tilts are illustrated in Fig. 1. After characterization of responses to vestibular stimulation was completed, 83 mg of CuSO₄ dissolved in 10 ml of distilled water was injected into the stomach. Five minutes following the intragastric administration of CuSO₄, the vestibular stimulation protocol described above was repeated. CuSO₄ is not absorbed into the bloodstream in the stomach (Zimnicka et al. 2011), and was only present in the stomach for 10–15 minutes. Since gastric emptying requires over 30 min in felines (Chandler et al. 1997; Chandler et al. 1999), it is unlikely that the significant quantities of CuSO₄ entered the intestine and reached intestinal transporters. These observations suggest that the effects of CuSO₄ could be reversed following recordings from each neuron by aspiration and a series of washes using distilled water.

Neural activity recorded during whole-body rotations was binned (500 bins/cycle) and averaged over the sinusoidal stimulus period. Sine waves were fitted to responses with the use of a least-squares minimization technique (Schor et al. 1984) executed using MATLAB (MathWorks, Natick, MA). The response sinusoid was characterized by two parameters: phase shift from the stimulus sinusoid (subsequently referred to as phase) and amplitude relative to the stimulus sinusoid (subsequently referred to as gain). We used one primary criterion and two secondary criteria to determine if neuronal activity was modulated by rotations (Jian et al. 2002; Miller et al. 2009; Destefino et al. 2011). First, responses were considered significant only if the signal-to-noise ratio (calculated as in (Schor et al. 1984)) was > 0.5. Data meeting this criterion were considered to represent real modulation of neuronal activity if only the first harmonic was prominent and the responses were consistent from trial to trial.

Near the end of recording sessions, lesions were made at defined coordinates by passing a 200- μ A negative current through the recording electrode for 60s. After euthanasia, the brainstem and cerebellum were removed, fixed in 10% formaldehyde, embedded in agar, cut transversely at 100- μ m thickness using a freezing microtome, mounted serially on slides, counterstained using thionine, and coverslipped. Sections were photographed using a 2X objective of a Nikon Eclipse E600N photomicroscope equipped with a Spot RT monochrome digital camera (Diagnostic Instruments, Sterling Heights, MI) and MetaMorph imaging software (Universal, Downingtown, PA). Montages of images were assembled using PTGui-Pro photostitching software (New House Internet Services B-V, The Netherlands). Recording sites were reconstructed on image montages with reference to the locations of electrolytic lesions, the relative positions of electrode tracks, and microelectrode depths.

Statistical comparisons of data were performed using Prism 6 software (GraphPad software, San Diego, CA). Statistical significance was assumed if $P < 0.05$. Pooled data are presented as mean $\pm$ SE.

Results

Responses to whole-body rotations in vertical planes were compared before and after the intragastric administration of CuSO_4 for 52 units whose locations were histologically confirmed in the rostral fastigial nucleus. We initially determined the response vector orientation for each neuron through the use of the wobble stimulus. Response vector orientations could be ascertained for 34 of the neurons. The activity of the other 18 units (35% of the fastigial nucleus neurons sampled) was robustly modulated by wobble rotations in one direction (clockwise or counterclockwise), but not the other. Such complex responses have been shown to result from spatiotemporal convergence (STC), or convergence of vestibular inputs with different spatial and temporal characteristics (e.g., inputs from otolith organs activated by ear-down rotations and semicircular canals activated by nose-up or nose-down rotations) (Baker et al. 1984; Schor et al. 1984; Schor and Angelaki 1992). In particular, units whose gains of responses to clockwise and counterclockwise wobble stimuli consistently deviated $> 2:1$ were classified as STC neurons. Examples of STC responses of one neuron are illustrated in Fig. 2. For this neuron, the gains of responses to clockwise rotations were 3.2 times larger than the gains of responses to counterclockwise rotations prior to CuSO_4 administration, and 2.6 times larger after the compound was injected into the stomach. The 18 neurons that initially exhibited STC responses to vestibular stimulation retained similar responses following the injection of CuSO_4 ; the median ratio of gains of responses to clockwise and counterclockwise wobble stimulation (higher gain response/lower gain response) was 3.4 before CuSO_4 was provided and 2.9 afterwards ($p = 0.79$, Wilcoxon matched-pairs signed rank test). In addition, one neuron acquired STC responses following the administration of CuSO_4 : the ratio of gains of responses to clockwise and counterclockwise stimulation changed from 1.26 to 9.36 after the compound was placed in the stomach.

The response vector orientations for the 34 fastigial nucleus neurons that lacked STC responses are indicated in Fig. 3A. Of these neurons, 15 (44%) had response vector

orientations near (within 45°) of ipsilateral ear-down roll, 5 (15%) had response vector orientations near contralateral ear-down roll, 7 (20.5%) had response vector orientations near nose-up pitch, and 7 (20.5%) had response vector orientations near nose-down pitch. Dynamic properties of responses to vestibular stimulation were determined by delivering sinusoidal rotations at multiple frequencies in a plane aligned near the response vector orientation. Examples of responses to sinusoidal single-plane tilts are provided in Fig. 1. Bode plots illustrating response gains and phase shifts between stimuli and sine waves fit to responses are shown in Fig. 4. Bode plots were generated for 27 of the 34 neurons for which response vector orientations were determined; the other seven neurons did not respond to low-frequency rotations (signal-to-noise ratios for responses were < 0.5), such that data could not be obtained across an entire decade of frequencies. As in a previous study (Jian et al. 2002), units were divided into two groups: those whose response gains increased < 7 -fold per stimulus decade (Fig. 4A), and those whose response gains increased over 7-fold per stimulus decade (Fig. 4B). Prior to administration of CuSO_4 , 18 neurons were included in the former group (gain increase < 7 -fold per stimulus decade), and 9 were included in the latter group (gain increase > 7 -fold per stimulus decade). Response phases for the neurons whose response gains increased < 7 -fold per stimulus decade led stimulus position modestly: $43 \pm 13^\circ$ at 0.5 Hz and $29 \pm 17^\circ$ at 1 Hz. Phase advances were larger for neurons whose response gains increased > 7 -fold per stimulus decade: $109 \pm 11^\circ$ at 0.5 Hz and $92 \pm 14^\circ$ at 1 Hz.

Following the administration of CuSO_4 , the responses to vestibular stimulation of five neurons were attenuated. The gains of responses to wobble stimulation for these five neurons were 154–405% (median of 207%) larger prior to administration of CuSO_4 than after the compound was present in the stomach. The gains of the responses to vestibular stimulation of the rest of the neurons changed $< 30\%$ after CuSO_4 was provided. Furthermore, CuSO_4 administration had little effect on the spatial and temporal properties of neuronal responses to vestibular stimulation. Fig. 3B indicates the change in response vector orientation following CuSO_4 injection. The median alteration in response vector orientation was 4° , with only two neurons having response vector orientations varying more than 45° . Fig. 4 shows that the gains and phases of responses to vestibular stimulation were similar before and after the administration of CuSO_4 . A two-way ANOVA (factors were stimulus frequency and presence of CuSO_4) confirmed that administration of the compound did not significantly affect response dynamics (see Fig. 4 for P values).

We also considered whether the spontaneous firing rates of neurons were altered by the intragastric infusion of CuSO_4 . The firing rates of nine of the 52 units decreased $> 30\%$ following administration of the compound, with the firing rates of six of these units dropping $> 50\%$; an example is provided in Fig. 5. The changes in firing rate typically developed 60–90 sec after placing CuSO_4 into the stomach, and were not correlated with alterations in blood pressure. The firing rates of two neurons increased over 50% after the administration of CuSO_4 , with the firing rates of the other 41 neurons changing $< 30\%$.

Intragastric injection of CuSO_4 resulted in $> 50\%$ attenuation of responses to vestibular stimulation for four of the six neurons whose spontaneous firing rates also decreased $> 50\%$. However, the other two neurons whose responses to vestibular stimulation were affected by

CuSO₄ (one neuron whose responses were attenuated, one neuron that acquired STC responses) exhibited little accompanying change in spontaneous firing rate. Fisher's exact test confirmed that fastigial nucleus neurons whose firing rates decreased >50% following the administration of CuSO₄ were more likely than other fastigial nucleus neurons to exhibit altered responses to vestibular stimulation ($P=0.0008$).

Discussion

The primary finding of this study was that irritation of the stomach lining using the intragastric injection of CuSO₄ produced a change in firing rate of a small fraction of rostral fastigial nucleus neurons (the firing rate was altered over 50% for 8/52 units, with most of these cells exhibiting a drop in firing rate). Those cells whose firing rate decreased following the administration of CuSO₄ typically also exhibited depressed responses to vestibular stimulation. These findings extend previous observations that visceral inputs are transmitted to the cerebellar fastigial nucleus (Somana and Walberg 1979; Zheng et al. 1982; Shapiro and Miselis 1985; Okahara and Nisimaru 1991; Tong et al. 1993; Saab and Willis 2001) by showing that these signals can alter the processing of labyrinthine inputs by fastigial nucleus neurons.

However, the fraction of rostral fastigial nucleus neurons whose gains of responses to vestibular stimulation were affected by the administration of CuSO₄ was lower than for regions of the brainstem that participate in generating nausea and vomiting. In particular, intragastric injection of CuSO₄ resulted in a >50% alteration in the magnitude of responses to vestibular stimulation of 28/51 (55%) parabrachial nucleus neurons (Suzuki et al. 2012), 8/22 (36%) lateral tegmental field neurons (Moy et al. 2012), and 16/49 (33%) neurons in the caudal aspect of the vestibular nucleus complex (Arshian et al. 2013), but less than 10% fastigial nucleus neurons ($p < 0.0001$, χ^2 test). Furthermore, the spatial and temporal properties of responses to vestibular stimulation of the vast majority of fastigial nucleus neurons were unaffected after CuSO₄ was placed in the stomach. These observations cast doubt on the notion that nauseogenic visceral inputs modulate motion sickness susceptibility through neural pathways that include the cerebellar fastigial nucleus. Instead, it seems likely that convergence of gastrointestinal and vestibular inputs occurs mainly in the brainstem, where the former signals modify the processing of the latter ones.

A secondary goal of these experiments was to ascertain whether decerebration alters the responses of fastigial nucleus neurons to vestibular stimulation in felines. In a previous study, we considered the responses of rostral fastigial nucleus neurons to vestibular stimulation in conscious cats (Miller et al. 2008b). The experiments reported in this manuscript were conducted using the same equipment and rotational paradigms employed in this previous study. A comparison of Bode plots generated from data collected in the two sets of experiments showed that the temporal properties of responses of fastigial nucleus neurons to vestibular stimulation were similar in decerebrate and conscious cats. However, the spatial properties of responses were quite different. In particular, most rostral fastigial nucleus neurons were preferentially activated by pitch rotations in conscious felines, but by roll rotations in decerebrate cats, as illustrated in Fig. 6. The mean deviation in response vector orientation from the pitch axis was 29° in conscious animals, but 47° in decerebrate

felines. These values were significantly different ($p=0.0008$, Mann-Whitney test). Furthermore, many fastigial nucleus neurons exhibited STC responses in decerebrate animals (18/52 units sampled), but not in conscious animals (2/47 units sampled) (Miller et al. 2008b). The fraction of fastigial nucleus neurons with STC responses was significantly different between the two preparations ($p<0.0001$, Fisher's exact test).

These findings show that decerebration affects the processing of labyrinthine signals by cerebellar neurons. Since STC responses are due to the convergence of vestibular inputs with different spatial and temporal properties (Baker et al. 1984; Schor et al. 1984; Schor and Angelaki 1992), the presence of these responses in decerebrate cats, but not conscious animals, suggests that some of the pathways relating vestibular signals to the cerebellum are suppressed in the conscious preparation. Similarly, another study indicated that the responses to vestibular stimulation of neurons in the rostral ventrolateral medulla that participate in cardiovascular regulation are exaggerated in decerebrate cats (Destefino et al. 2011). Other studies compared responses to whole-body rotations of neurons in the caudal vestibular nuclei in decerebrate (Endo et al. 1995; Arshian et al. 2013) and conscious felines (Miller et al. 2008a; McCall et al. 2013) and reported little difference in findings between the preparations. Hence, it appears that decerebration is more likely to unmask responses to vestibular stimulation in brain regions that receive multisynaptic inputs from the labyrinth than areas that receive inputs directly from the inner ear.

This line of reasoning validates our conclusion that the cerebellar fastigial nucleus does not play a principal role in modulating motion sickness susceptibility when animals are nauseated by an emetic stimulus. The amplification of signals and unmasking of pathways in the decerebrate preparation seemingly would increase the potential for the intragastric injection of CuSO_4 to affect the processing of labyrinthine signals by fastigial nucleus neurons. Since CuSO_4 administration affected the responses to vestibular stimulation of only a small fraction of fastigial nucleus neurons in decerebrate cats, it is unlikely that the effects would be more prominent in conscious animals.

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Figure 1.

Responses to whole-body rotations in the roll plane of a rostral fastigial nucleus neuron.

A,B: Unit activity recorded during table rotations at 0.5 Hz; **A** shows action potentials recorded from the neuron, whereas **B** illustrates table movement recorded using a potentiometer. **C–E:** Histograms illustrating averaged responses of the neuron to roll rotations at 0.1 Hz (**C**), 0.5 Hz (**D**), and 1.0 Hz (**E**). A sine wave fit to responses is superimposed on the tracings of neuronal firing rate. Blue sine waves indicate tilt table position. At every frequency, response phases led stimulus position (ipsilateral ear down tilt) by $\sim 90^\circ$. Response gain increased ~ 10 -fold as the stimulus frequency increased from 0.1 to 1.0 Hz. *Abbreviations:* CED, contralateral ear down tilt; IED, ipsilateral ear down tilt.

Figure 2.

Histograms illustrating averaged responses of a neuron to 5° clockwise (**A,B**) and counterclockwise (**C,D**) wobble stimuli delivered at 0.5 Hz, before (**A,C**) and after (**B,D**) the intragastric administration of copper sulfate (CuSO₄). A sine wave fit to responses is superimposed on the tracings of neuronal firing rate. Both prior and subsequent to administration of CuSO₄, the gains of responses to clockwise rotations (3.5 spikes/sec/° in **A**; 3.0 spikes/sec/° in **B**) were consistently over two times larger than the gains of responses to counterclockwise rotations (1.2 spikes/sec/° in **C**; 1.0 spikes/sec/° in **D**). Hence, the neuron was classified as having spatiotemporal convergence (STC) responses to vestibular stimulation. *Abbreviations:* CED, contralateral ear down tilt; IED, ipsilateral ear down tilt; ND, nose down tilt; NU, nose up tilt.

Figure 3.

A: Polar plots showing response vector orientations and gains of responses of fastigial nucleus neurons to whole-body rotations in vertical planes. Response vector orientations were determined using wobble stimuli delivered at 0.5 Hz. The maximal radius of each plot designates a response gain of 15 spikes/sec/°. The response vector orientations were plotted using a head-centered coordinate system, with 0° corresponding to ipsilateral ear-down (IED) roll tilt, 90° corresponding to nose-down (ND) pitch, 180° corresponding to contralateral ear-down (CED) roll, and -90° corresponding to nose-up (NU) pitch. **B:** Changes in response vector orientation following the intragastric injection of copper sulfate. Grey circles designate the difference in response vector orientation for each unit before and after the administration of CuSO₄. The long bar designates the mean change in response vector orientation, and error bars indicate one SEM. For all but two neurons, administration of copper sulfate resulted in <45° shift in response vector orientation.

Figure 4.

Bode plots illustrating the average dynamic properties of responses of fastigial nucleus neurons to rotations in a fixed vertical plane. Average Bode plots for neurons whose response gains increased < 7 -fold per stimulus decade are provided in **A**, whereas **B** shows responses for neurons whose response gains increased > 7 -fold per stimulus decade. Solid lines designate data collected prior to administration of copper sulfate, whereas dashed lines indicate responses following the intragastric injection of the compound. Response gains and phases were plotted with respect to stimulus position. Error bars indicate one SEM. P values in each panel indicate the probability that copper sulfate administration altered the responses (two-way ANOVA, factors were presence of copper sulfate and stimulus frequency).

Figure 5.

Effect of administration of copper sulfate (designated by arrow) on the spontaneous firing rate of a fastigial nucleus neuron. The top trace is a raster plot of unit activity, with each vertical line indicating the occurrence of an action potential. The bottom panel shows blood pressure. Approximately 70 sec following the administration of copper sulfate, the firing rate of the unit decreased substantially, although there was no correlated change in blood pressure.

Figure 6.

Comparison of response vector orientations of rostral fastigial nucleus neurons in conscious cats (data from (Miller et al. 2008b)) and decerebrate cats (data from this study). The deviation in response vector orientation from the pitch axis is indicated, such that the deviation for a neuron whose response vector orientation was aligned with the pitch axis was 0°, whereas the deviation for a neuron whose response vector orientation was aligned with the roll axis was 90°. Data for neurons that exhibited STC responses to rotations were excluded from the analysis. Horizontal lines designate mean values, whereas error bars indicate SEM.